

BRIEF REPORT

Low Incidence of Inflammatory Bowel Disease Adverse Events in Adalimumab Clinical Trials Across Nine Different Diseases

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Objective. Adalimumab is approved for treatment of Crohn's disease and ulcerative colitis. Thus, we postulated that exacerbation or new-onset of inflammatory bowel disease (IBD) would be rare events in patients treated with adalimumab for non-IBD indications. The objective was to evaluate the incidence of IBD adverse events (AEs) across adalimumab trials.

Methods. IBD AE rates in 75 adalimumab clinical trials in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, pediatric enthesitis-related arthritis, uveitis, hidradenitis suppurativa, adult and pediatric psoriasis, psoriatic arthritis, nonpsoriatic arthritis peripheral spondyloarthritis (SpA), axial SpA, including nonradiographic axial SpA, and ankylosing spondylitis, were analyzed. Search terms for IBD AEs (new onset or worsening/flare) included IBD, ulcerative colitis, Crohn's disease, and ulcerative proctitis.

Results. This analysis included 24,114 patients, representing 36,508 patient-years of adalimumab exposure. The overall rate of IBD AEs in adalimumab-treated patients was 0.1 (95% confidence interval [95% CI] 0.1–0.2)/100 patient-years (41 events), ranging from no events (psoriatic arthritis, uveitis, and pediatric trials) to 0.8 (95% CI 0.2–2.2)/100 patient-years in peripheral SpA. The rate of IBD in axial SpA was 0.6 (95% CI 0.4–1.0)/100 patient-years. During placebo-controlled trials, the overall IBD rate was 0.1 (95% CI 0.0–0.3)/100 patient-years for adalimumab groups (3 events in 6,781 patients; 2,752 patient-years of exposure) and 0.1 (95% CI 0.0–0.4)/100 patient-years for placebo groups (1 event in 3,493 patients; 1,246 patient-years of exposure). IBD rates in axial SpA were 0.5 (95% CI 0.1–1.4)/100 patient-years for adalimumab and 0.6 (95% CI 0.0–3.1)/100 patient-years for placebo.

Conclusion. The rates of IBD AEs in adalimumab clinical trials were generally low across the evaluated diseases, including axial SpA; all events occurred in adult patients.

INTRODUCTION

Tumor necrosis factor (TNF) and interleukin-17 (IL-17), among other cytokines, play a role in inflammatory bowel disease (IBD) and other immune-mediated inflammatory diseases (IMIDs) (1). Previous studies have shown that TNF contributes to intestinal inflammation

and is elevated in the serum and intestinal cells of patients with IBD (2). Monoclonal TNF inhibitors (i.e., adalimumab, infliximab, certolizumab, and golimumab) are effective for the treatment of IBD, while etanercept, a TNF receptor fusion protein, is not (3).

Similarly to TNF, IL-17 levels are increased in patients with IBD and contribute to intestinal inflammation by stimulating various cell

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SIGNIFICANCE & INNOVATIONS

- The results of this analysis of 75 adalimumab clinical trials in adult and pediatric patients demonstrated that the rates of inflammatory bowel disease (IBD) adverse events were generally low across non-IBD diseases, with all events occurring in adult patients.
- In patients with axial spondyloarthritis who have an increased risk of IBD, the rates of IBD events were comparable between adalimumab- and placebo-treated patients.
- Based on these data, adalimumab is a reasonable therapeutic option for patients who are eligible for a biologic therapy and who are at risk for development or worsening of IBD.

types to produce proinflammatory mediators (4). However, available data indicate that IL-17 inhibition (e.g., with a monoclonal antibody blocking IL-17A [secukinumab]) is both ineffective and may worsen IBD (5,6).

Adalimumab is approved for the treatment of 15 indications worldwide, including adult and pediatric Crohn's disease and adult ulcerative colitis. Therefore, exacerbations of existing or new-onset IBD may be rare events in patients treated with adalimumab for non-IBD indications. The overall rate of new onset or worsening of IBD across adalimumab clinical trials is unknown and is of particular interest in patients with axial spondyloarthritis (SpA) who have a high prevalence of both overt IBD and subclinical gut inflammation (7,8). The objective of this analysis was to report the incidence of IBD adverse events (AEs) in adalimumab clinical trials across indications, with a specific focus on IBD occurrence in patients with axial SpA, including patients with ankylosing spondylitis (AS) and nonradiographic axial SpA.

PATIENTS AND METHODS

Patients. This post hoc analysis assessed the rates of IBD AEs in patients with rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), pediatric enthesitis-related arthritis (ERA), uveitis (noninfectious intermediate, posterior, or pan-uveitis), hidradenitis suppurativa, adult and pediatric psoriasis (including nail psoriasis), psoriatic arthritis (PsA), non-PsA peripheral SpA, nonradiographic axial SpA, and AS, who participated in phase II through phase IV of interventional, adalimumab clinical trials (Table 1); patient data from registry, noninterventional, and real-world studies were not included in the analysis. Adalimumab trials conducted specifically in patients with Crohn's disease, ulcerative colitis, and intestinal Behçet's disease were excluded from this analysis. Gastrointestinal-related exclusion criteria varied by trial, ranging from a specific exclusion for active or unstable IBD (10 RA, 6 psoriasis, 2 nonradiographic axial SpA, 1 peripheral SpA, and 1 PsA trials) to less specific exclusions for unstable or poorly

controlled medical conditions or underlying conditions considered by the investigator as an unacceptable risk for trial participation. Thus, none of the trials included in this analysis excluded patients with a history of IBD. The presence of prevalent IBD at baseline was not systematically characterized for the entire study population in any of the trials. (For information on requesting data from AbbVie-sponsored studies, visit: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>).

Assessment of IBD. Data on IBD (new onset, worsening/flare) were collected as AEs reported throughout the duration of the trials and through 70 days (5 half-lives) after the last dose of adalimumab. The search criteria for IBD events included the following standardized Medical Dictionary for Regulatory Activities preferred terms (either new onset or worsening/flare): IBD, ulcerative colitis, Crohn's disease, IBD not otherwise specified, and ulcerative proctitis. Gastrointestinal perforation was outside the scope of the search criteria. The automated search did not distinguish between new-onset IBD and flare of preexisting IBD. A manual assessment to distinguish new-onset IBD and worsening of preexisting disease was performed for the events occurring in patients with axial SpA (AS and nonradiographic axial SpA).

Statistical analysis. IBD AEs (combined for new onset and flare) were reported as the number of patients with an IBD event, the total number of events (i.e., each event was recorded separately for patients with >1 event), and the number of events when censored after the first event. Rates of IBD events were calculated as events per 100 patient-years; 95% confidence intervals (95% CIs) were based on exact confidence limits from a Poisson distribution. IBD event rates were determined for all patients treated

Table 1. Number of clinical trials and patient exposure per diseases included in the analysis*

Disease	Trials, no.	Patients, no. (PY)
All adalimumab trials	75	24,114 (36,508)
RA	35	15,152 (24,813)
Psoriasis, adult	17	3,703 (5,409)
All SpA†	12	3,891 (4,363)
AS	5	2,026 (2,120)
Nonradiographic axial SpA	2	863 (855)
PsA	4	837 (998)
Peripheral SpA	1	165 (391)
Hidradenitis suppurativa	4	733 (836)
JIA‡	4	274 (797)
Uveitis	2	250 (167)
Psoriasis, pediatric	1	111 (122)

* Excludes adalimumab trials in Crohn's disease, ulcerative colitis, and Behçet's disease. AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient-years; SpA = spondyloarthritis; RA = rheumatoid arthritis.

† Includes patients with PsA, peripheral SpA, nonradiographic axial SpA, and AS from interventional adalimumab trials.

‡ Includes patients with polyarticular JIA and pediatric enthesitis-related arthritis from interventional adalimumab trials.

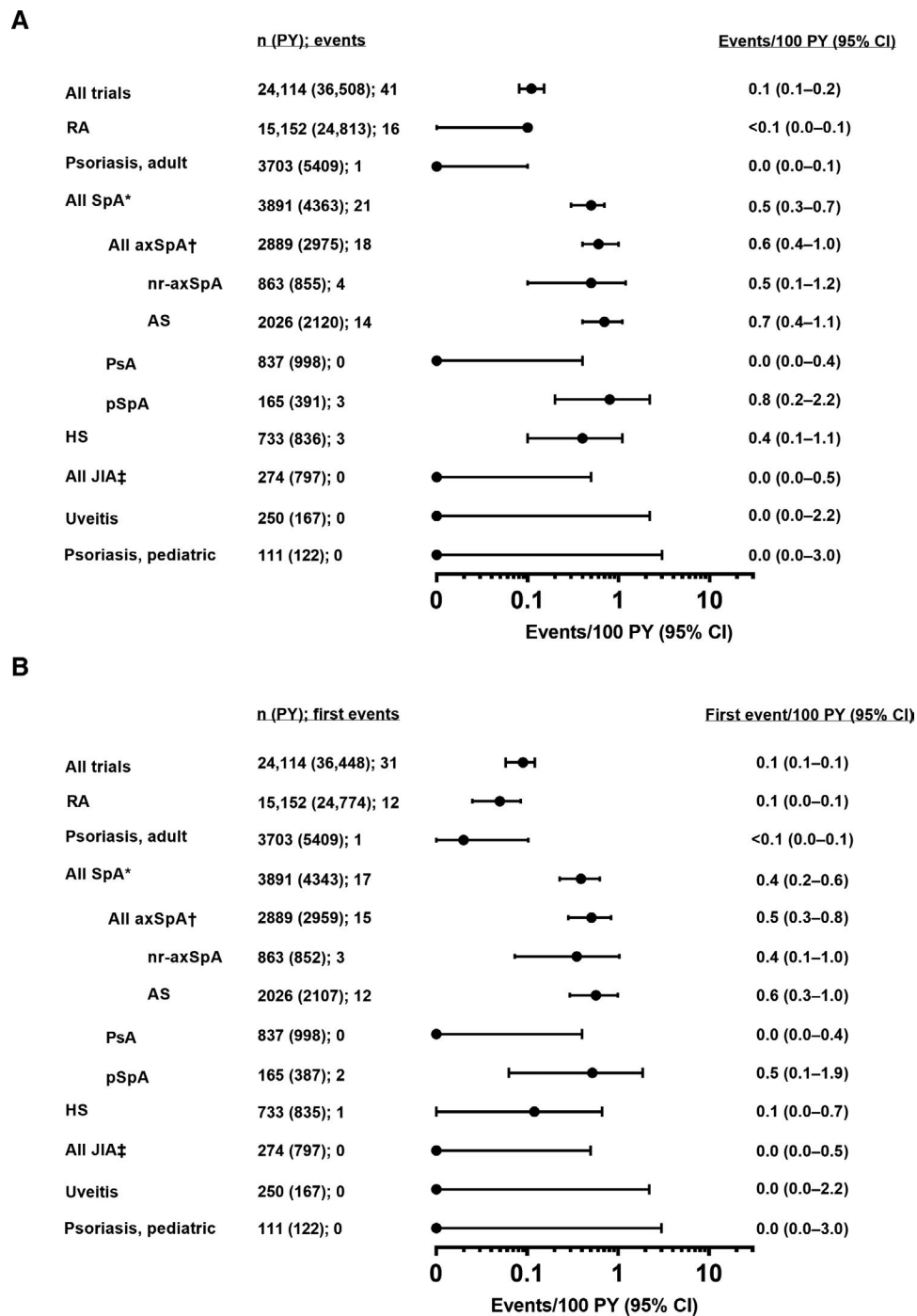


Figure 1. Patients treated with adalimumab in clinical trials, including long-term extensions. Excludes patient data from registry, noninterventional, real-world studies and from adalimumab trials in Crohn's disease, ulcerative colitis, and Behçet's disease. **A**, Rates of all inflammatory bowel disease (IBD) events per 100 patient-years (PY). **B**, Rates of first IBD events only per 100 patient-years (with patients censored after first event). 95% CI = 95% confidence interval; * = includes patients with psoriatic arthritis (PsA), non-PsA peripheral spondyloarthritis (pSpA), nonradiographic axial SpA (nr-axSpA), and ankylosing spondylitis (AS) from interventional adalimumab trials; † = includes patients with nonradiographic axial SpA and AS from interventional adalimumab trials; ‡ = includes patients with polyarticular juvenile idiopathic arthritis (JIA) and pediatric enthesitis-related arthritis from interventional adalimumab trials; HS = hidradenitis suppurativa; RA = rheumatoid arthritis.

with adalimumab during the studies (any adalimumab population, patients who received at least 1 dose of adalimumab), as well as separately for placebo- and adalimumab-treated patients during the placebo-controlled periods.

To improve comparability between the studies with otherwise varying durations of follow-up, and given the potential for a time-varying hazard of IBD events, the event rate of IBD events over the first 1-year period in each trial was also calculated

(patients initially receiving placebo were included at the time of first adalimumab dose up to year 1).

RESULTS

This analysis included 75 interventional adalimumab clinical trials in 24,114 patients, representing 36,508 patient-years of adalimumab exposure (Table 1). The largest exposure was in patients with RA (15,152 patients; 24,813 patient-years). A total of 2,026 patients from AS studies (2,120 patient-years) and 863 patients from nonradiographic axial SpA studies (855 patient-years) were included.

Overall, 41 IBD events (rate of 0.1/100 patient-years) were reported across all trials (Figure 1A). The rates of IBD events varied across diseases, ranging from no IBD events (PsA, uveitis, and pediatric indications) to 0.8/100 patient-years (peripheral SpA) (Figure 1A). Thirty-one patients experienced an IBD event, corresponding to an overall IBD rate of 0.1/100 patient-years when patients were censored after the first event (Figure 1B).

Across the axial SpA trials, corresponding to 2,889 patients and 2,975 patient-years of exposure, the rate of IBD in adalimumab-treated patients was 0.6/100 patient-years (18 events), 14 events (0.7/100 patient-years) in 12 patients with AS, and 4 events (0.5/100 patient-years) in 3 patients with nonradiographic axial SpA (Figure 1A). In patients with AS, the 14 IBD events consisted of 7 new-onset events and 7 flares, and in patients with nonradiographic axial SpA, the 4 IBD events consisted of 4 flares. Among the 15 patients with an IBD event, 5 patients with AS and all 3 patients with nonradiographic axial SpA had a prior history of IBD; none of these 15 patients prematurely discontinued from the trial. A total of 34 patients with AS and 30 patients with nonradiographic axial SpA had IBD at baseline (past or present); 15% (5 of 34) and 10% (3 of 30) of these patients, respectively, or 13% (8 of 64) overall experienced a flare during the adalimumab studies.

During the placebo-controlled periods, which ranged from 5 to 80 weeks (most commonly 12 or 24 weeks), 3 IBD events (0.1/100 patient-years) in 3 patients were reported with adalimumab (among 6,781 patients; 2,752 patient-years of exposure) and 1 event (0.1/100 patient-years) with placebo (among 3,493 patients; 1,246 patient-years of exposure) (Figure 2). All these events were reported in patients with axial SpA, corresponding to 0.5/100 patient-years (nonradiographic axial SpA, 2 events in 2 patients; AS, $n = 1$) with adalimumab and 0.6/100 patient-years (nonradiographic axial SpA, $n = 1$) with placebo. No IBD events were reported in pediatric trials or in adult trials of RA, psoriasis, PsA, peripheral SpA, uveitis, and hidradenitis suppurativa during the placebo-controlled periods (Figure 2).

The rate of IBD events occurring over 1 year of adalimumab exposure across all trials was 0.1 (95% CI 0.1–0.2)/100 patient-years. The 1-year rate of IBD events was 0.5 (95% CI 0.2–0.9)/100 patient-years for the overall SpA group and 0.6 (95% CI 0.3–1.2)/100 patient-years for patients with axial SpA (0.5 [95% CI

0.1–0.6]/100 patient-years for AS, and 0.7 [95% CI 0.2–1.5]/100 patient-years for nonradiographic axial SpA). The 1-year rate of IBD events was <0.1 (95% CI 0.0–0.1)/100 patient-years in RA and 0.0 (95% CI 0.0–0.2)/100 patient-years in adult psoriasis trials (1 IBD event). No IBD events were reported during the 1-year period in all the other adult populations (i.e., PsA, uveitis, hidradenitis suppurativa), as well as in pediatric psoriasis and all JIA (polyarticular JIA and pediatric ERA).

The majority of the 41 IBD events reported across trials were not serious events; only 9 serious IBD AEs were observed (5 flares and 4 new-onset events), none of which were life threatening or led to death. Of these, 4 events were observed in RA trials, 3 events in AS trials, 1 event in the peripheral SpA trial, and 1 event in a hidradenitis suppurativa trial.

DISCUSSION

This analysis of 75 adalimumab clinical trials in >24,000 adult and pediatric patients and 36,508 cumulative patient-years of exposure to adalimumab demonstrated that the rates of IBD AEs were generally low in adalimumab-exposed patients across diseases and comparable to the rates observed in placebo-treated patients. Furthermore, all events occurred in adult patients, and no IBD events were noted in adult patients with PsA or uveitis.

IMIDs are a broad group of diseases that share common inflammatory pathways, and multiple IMIDs commonly may coexist within a patient (1,7,9,10). IBD is a relatively common extraarticular manifestation in certain IMIDs, such as the SpA family of diseases. For AS and nonradiographic axial SpA specifically, 5–10% of patients are estimated to be affected by overt IBD, with subclinical disease observed in up to 60% of patients (7,8). In our analyses, the rate of IBD-related AEs (both flares and new-onset events) in patients with axial SpA (nonradiographic axial SpA and AS) was low, with 18 events reported in 2,889 patients, representing 2,975 patient-years of exposure to adalimumab (0.6/100 patient-years [95% CI 0.4–1.0]). Furthermore, the rates of IBD AEs in patients with axial SpA were similar for adalimumab and placebo groups during the placebo-controlled periods (0.5/100 patient-years versus 0.6/100 patient-years). The incidence of IBD AEs was numerically slightly higher in AS than nonradiographic axial SpA, 0.7/100 patient-years versus 0.5/100 patient-years, respectively, but the confidence intervals were overlapping (Figure 1).

In an earlier meta-analysis of TNF inhibitor clinical trials, the pooled incidence rate of new onset/worsening of IBD in placebo-treated patients with AS was 1.3/100 patient-years (95% CI 0.2–4.8; 150 patient-years), while in patients treated with TNF inhibitors infliximab, etanercept, or adalimumab, the rates, respectively, were 0.2/100 patient-years (95% CI 0–0.9; 618 patient-years), 2.2/100 patient-years (95% CI 1.2–3.8; 625 patient-years), and 2.3/100 patient-years (95% CI 0.5–6.6; 132 patient-years) (11). Based on data from 2,026 patients representing 2,120 patient-years of adalimumab exposure, the rate of IBD in patients with

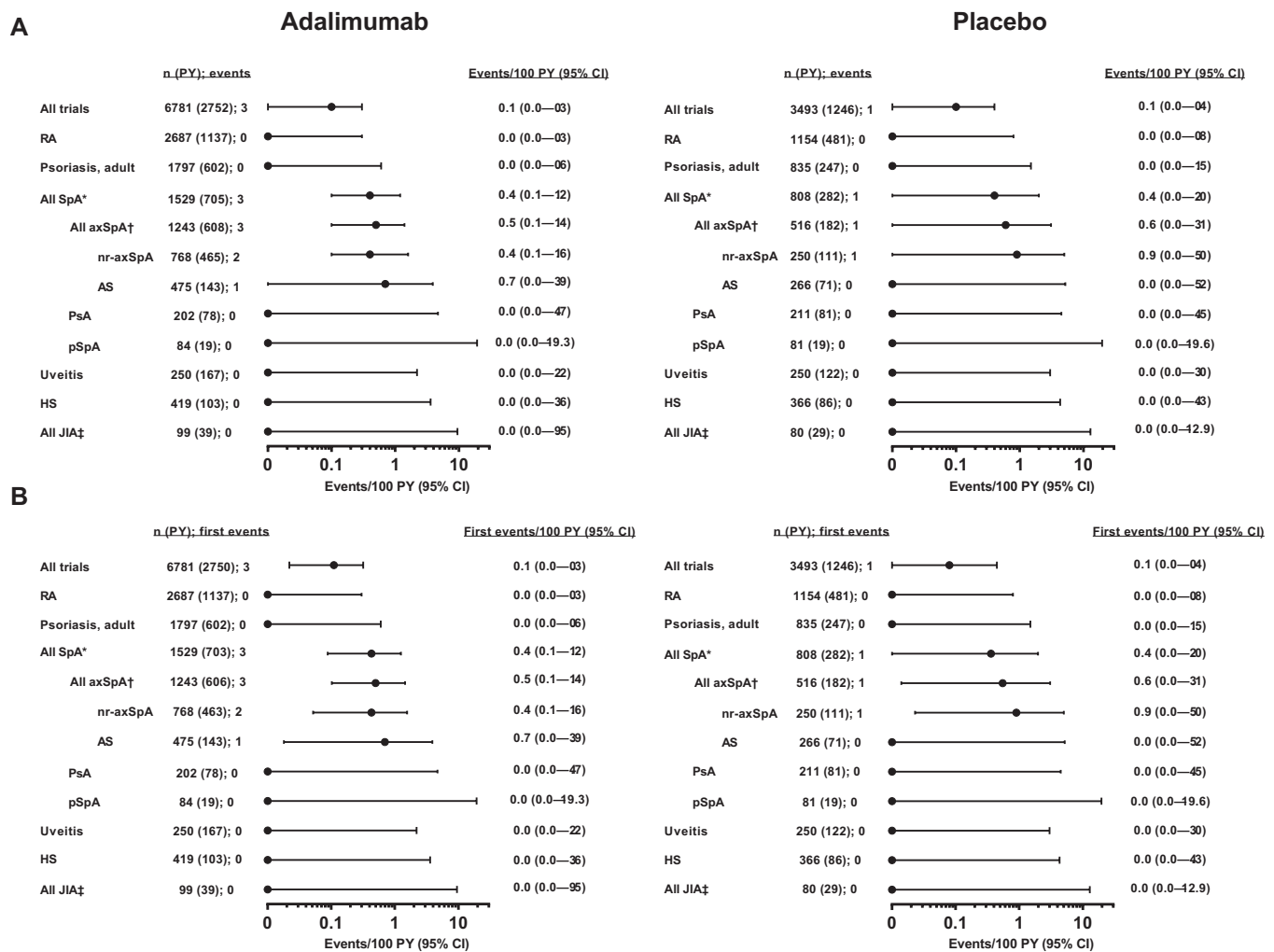


Figure 2. Patients from placebo-controlled period of adalimumab clinical trials across diseases. Excludes adalimumab trials in Crohn's disease, ulcerative colitis, and Behçet's disease. **A**, Rates of all inflammatory bowel disease (IBD) events as incidence per 100 patient-years (PY). **B**, First IBD events only per 100 patient-years (with patients censored after first event). Duration of placebo periods were 5 weeks (1 study), 12 weeks (13 studies), 16 weeks (4 studies), 24 weeks (10 studies), 26 weeks (1 study), 32 weeks (1 study), 40 weeks (1 study), 52 weeks (1 study), and up to 80 weeks (2 studies). 95% CI = 95% confidence interval; * = includes patients with psoriatic arthritis (PsA), non-PsA peripheral spondyloarthritis (pSpA), nonradiographic axial SpA (nr-axSpA), and ankylosing spondylitis (AS) from interventional adalimumab trials; † = includes patients with nonradiographic axial SpA and AS from interventional adalimumab trials; ‡ = includes patients with polyarticular juvenile idiopathic arthritis (JIA) and pediatric enthesitis-related arthritis from interventional adalimumab trials; HS = hidradenitis suppurativa; RA = rheumatoid arthritis.

AS observed in the present analysis (0.7/100 patient-years [95% CI 0.4–1.1]) was lower than in that earlier analysis, which included only 1 randomized clinical trial (that was also included here) and 1 small open-label study.

No newer data comparing the incidence of IBD AEs in patients with axial SpA receiving nonbiologic versus biologic therapy have been published. In the Be-Giant cohort of patients with axial SpA fulfilling the Assessment of SpondyloArthritis international Society classification criteria (12), the combined incidence rate of flares and new onset IBD was 1.64/100 patient-years (95% CI 0.74–3.11) for nonbiologic versus 2.73/100 patient-years (95% CI 1.00–5.95) for biologic therapy (A. De Craemer and D. Elewaut personal

communication). These incidence rates are much higher than in our analysis of adalimumab axial SpA trials. Similarly, the percentage of patients who experienced at least 1 IBD flare was higher in the Be-Giant cohort versus the pooled adalimumab axial SpA trial population (33% versus 13%), although baseline IBD prevalence was similar (6% versus 5%). However, drawing conclusions based on this comparison is difficult, because the total number of axial SpA patients included in the Be-Giant cohort to date is relatively low, and the total follow-up duration is relatively short (269 patients with a total of 769 patient-years follow-up). Furthermore, channeling bias cannot be ruled out because patients with more active/severe IBD could be preferentially started on biologic therapy in general practice.

Patients with PsA and psoriasis, who share similar inflammatory disease pathways with the greater SpA family, are also at increased risk of concomitant IBD (9,10). Up to 33% of patients with PsA may have bowel involvement (overt or subclinical) (9), and the incidence rate (unspecified whether new onset or flare) in patients with psoriasis and PsA of Crohn's disease (0.032 and 0.057 per 100 patient-years, respectively) and ulcerative colitis (0.079 and 0.11 per 100 patient-years, respectively) was higher compared with the general population (Crohn's disease 0.017/100 patient-years; ulcerative colitis 0.045/100 patient-years) (10). In our analysis, no IBD cases were observed among patients with PsA, and only 1 event (0.0/100 patient-years) was observed in adult patients with psoriasis.

Because IL-17 inhibition is a therapeutic option for patients with psoriasis, PsA, and AS (patients who are at increased risk of IBD as a manifestation of their disease), it is relevant to discuss findings for drugs with this mechanism of action. Clinical trial data for the IL-17 inhibitor secukinumab suggest no benefit and possible worsening of Crohn's disease (5). The potential risk of Crohn's disease and ulcerative colitis events after secukinumab exposure was demonstrated in real-world databases (13), and product labeling recommends caution when treating patients with AS, PsA, or psoriasis who also have IBD due to risk of IBD exacerbation (6). A recent pooled analysis of 10 secukinumab studies across these 3 indications reported Crohn's disease and ulcerative colitis incidence rates for patients with psoriasis ($n = 3,430$) of 0.11/100 patient-years (3 events total; 3 flares) and 0.15/100 patient-years (4 events total; 2 flares), respectively; for patients with PsA ($n = 974$), 0.07/100 patient-years (1 event total; 0 flares) and 0.14/100 patient-years (2 events total; 1 flare), respectively; and for patients with AS ($n = 591$), 0.77/100 patient-years (8 events total; 3 flares) and 0.29/100 patient-years (3 events total; 1 flare), respectively. Patients with active IBD were excluded from the studies (14). An additional pooled analysis of data from the subset of 3 MEASURE trials in 794 patients (1,706 patient-years) with AS receiving secukinumab for up to 3 years found an IBD rate of 0.7/100 patient-years (15). However, these reports did not specify the severity of IBD AEs in the secukinumab trials. In our analysis, only 9 of 41 IBD AEs across 75 adalimumab trials were serious; 3 occurred in patients with AS, and none in patients with nonradiographic axial SpA. Further, none of the 15 axial SpA patients who experienced IBD AEs prematurely discontinued from the trial. Risks of new onset or worsening of IBD are largely unknown for other biologic therapies that may work along the IBD pathway.

The strengths of this analysis include the fact that IBD data were obtained from a large, well-characterized clinical trial database and included a comparison versus placebo, although placebo-controlled periods were limited. The limitations of our analysis include lack of systematic identification of concomitant IBD at baseline in diseases other than axial SpA to distinguish new IBD onsets from IBD flares. AE reporting was the mechanism used to identify IBD events, and AEs were not systematically confirmed by

additional diagnostic procedures. This analysis also did not include nonspecific terms that may be related to IBD (such as diarrhea, blood in stool, etc.) because doing so would overestimate the true IBD incidence. It would be useful to know whether subclinical gut inflammation, common in patients with SpA, existed at baseline in patients with new-onset IBD occurring during the trials, but this information was not collected.

In conclusion, the rates of IBD AEs in adalimumab trials were generally low across diseases. In patients with axial SpA, who are known to be at an increased risk of IBD, the rates of IBD events were comparable between adalimumab- and placebo-treated patients, as well as with published pooled placebo rates across multiple AS clinical trials with TNF inhibitors. Based on the observed low rates of IBD and its approved indications for Crohn's disease and ulcerative colitis, adalimumab is a reasonable therapeutic option for patients who are eligible for a biologic therapy and who are at risk for development or worsening of IBD. This analysis provides a benchmark for IBD AEs that other therapies, now and in the future, might be compared against.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Elewaut had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Elewaut, Anderson, Hojnik, Curtis.

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ROLE OF THE STUDY SPONSOR

AbbVie funded the studies, contributed to their design, and was involved in the collection, analysis, and interpretation of the data, and in the writing and review. Debanjali Dasgupta, PhD, of AbbVie, and Jen-fue Maa, PhD, formerly of AbbVie, provided statistical analysis support. Medical writing support was provided by Maria Hovenden, PhD, and Janet E. Matsuura, PhD, of Complete Publication Solutions, LLC (North Wales, PA), a CHC Group company, and was funded by AbbVie. Publication of this article was contingent upon approval by AbbVie.

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